IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	**MDL No. 2:14-mn-02502-RMG**
	)	**This document relates to:**
	)	*Juanita Hempstead v. Pfizer Inc.*, 2:14-cv-01879-RMG

PFIZER'S REPLY IN SUPPORT OF ITS MOTION TO EXCLUDE THE EXPERT TESTIMONY OF ELIZABETH J. MURPHY, M.D., D.PHIL.

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Plaintiffs ask the Court to simply take their word that Dr. Murphy carefully applied a reliable methodology (which they describe for the first time as differential diagnosis) in forming her causation opinion in this case. What is missing is actual evidence to support that claim.

On the contrary, the record confirms that Dr. Murphy did not perform a reliable differential diagnosis. In particular, Dr. Murphy failed: (1) to consider and to rule out numerous alternative causes of Ms. Hempstead's diabetes; (2) to come forward with any reliable basis to conclude that those alternative causes were not sufficient on their own to account for Ms. Hempstead's diabetes; and (3) to rule in Lipitor as a potential cause. Rather, Dr. Murphy's specific causation opinion is based on nothing more than her belief that Lipitor increases the risk of diabetes on a population basis and the presence of a vague temporal relationship between Ms. Hempstead's Lipitor use and her diabetes diagnosis, evidence that is wholly insufficient to support her opinion in this case. Accordingly, Pfizer respectfully requests that the Court exclude the specific causation testimony of Dr. Elizabeth Murphy.

I. DR. MURPHY'S OPINION IS NOT THE PRODUCT OF A RELIABLE DIFFERENTIAL DIAGNOSIS.

Plaintiffs claim that Dr. Murphy's opinion that Lipitor was a "substantial contributing factor" and "but-for cause" of Ms. Hempstead's diabetes is admissible because she "performed a differential diagnosis to form her opinion."[1] Plaintiff's Memorandum in Opposition to Pfizer, Inc.'s Motion to Exclude the Expert Testimony of Elizabeth J. Murphy, M.D., D.Phil., ECF No. 1094 ("Opp.") at 8. But, as discussed below, Dr. Murphy's opinion is not the product of a reliable differential diagnosis process. On the contrary, it is a "wholly conclusory finding based upon [her] subjective beliefs rather

[1] Plaintiffs acknowledge that Dr. Murphy is not offering an opinion that, absent taking Lipitor, Ms. Hempstead never would have developed diabetes. Rather, Dr. Murphy appears to claim that Lipitor accelerated Ms. Hempstead's diabetes diagnosis—that she would not have been diagnosed with diabetes "at that time" (in May 2004). Opp. at 12.

than any valid scientific method." *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 200 (4th Cir. 2001).

As a threshold matter, while Plaintiffs assert that Dr. Murphy's methodology was differential diagnosis, Dr. Murphy did not make a similar claim either in her report or at deposition. Nor did Dr. Murphy suggest that her methodology is used by anyone outside of the courtroom, or even described in any medical or scientific publication or statement. Murphy Tr. (Ex. 3) at 166:13-24, 170:1-9.[2] Rather, Dr. Murphy indicated that, in preparing her report, she "looked at the criteria" used by Pfizer's experts in their general causation reports submitted in this litigation and found them to be consistent with her analysis. *Id*. at 166:7-167:17. None of those reports apply, or even discuss, a differential diagnosis methodology.[3]

That having been said, even if we assume *arguendo* that Dr. Murphy attempted to perform a differential diagnosis, it does not necessarily follow that her opinion is admissible under *Daubert*. As the Eleventh Circuit stated in *McClain*, "an expert does not establish the reliability of his techniques or the validity of his conclusions simply by claiming that he performed a differential diagnosis on a patient." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1253 (11th Cir. 2005). In other words, simply invoking the words "differential diagnosis" is not a magic key that opens the *Daubert* gates.

"A reliable differential diagnosis . . . generally is accomplished by determining the possible causes for the patient's symptoms and then eliminating each of these potential causes until reaching

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[2] Exhibits 1-25 refer to the exhibits submitted with Pfizer's opening brief [ECF No. 1006].

[3] It is also worth noting that, contrary to Plaintiffs' claim, none of Pfizer's specific causation experts used a differential diagnosis methodology or opined as to the cause of Ms. Hempstead's diabetes. Rather, each of those experts found that, given the scientific evidence, the nature of the diabetes disease process, and Ms. Hempstead's numerous risk factors, there was no reliable basis to conclude that Lipitor played any role in her developing diabetes. Indeed, Dr. Waikar specifically stated: "I am not aware of any methodologically sound or generally recognized means by which one can conclude that [Lipitor] therapy contributed to Ms. Hempstead's development of diabetes." Waikar Rep. (Ex. 26) at 6.

one that cannot be ruled out or determining which of those that cannot be excluded is the most likely." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 262 (4th Cir. 1999). While an expert need not rule out all possible alternative causes, the expert must "take serious account" of all potential alternative causes and provide a reasonable basis for her opinion that those alternative causes were "not the sole cause" of plaintiff's injury. *Cooper*, 259 F.3d at 202; *see also Guinn v. AstraZeneca Pharms. LP*, 602 F.3d 1245, 1253 (11th Cir. 2010). Dr. Murphy's analysis in this case falls well short of this standard.

A. Dr. Murphy Did Not Consider A Number Of Significant Potential Alternative Causes Of Ms. Hempstead's Diabetes.

As Pfizer explained in its opening brief, Dr. Murphy did not consider, let alone rule out, a number of Ms. Hempstead's significant diabetes risk factors, including blood glucose levels in the prediabetic range, metabolic syndrome, and adult weight gain. Plaintiffs offer a variety of arguments to allay this significant methodologic flaw in her analysis, but, as discussed below, each fails as a matter of fact, science, and/or law.

First, citing to the Fourth Circuit's decision in *Cooper*, Plaintiffs suggest that Dr. Murphy's failure to consider these potential alternative causes should go to the weight and not the admissibility of her testimony. Opp. at 20. Plaintiffs are correct to the extent that in *Cooper* the Fourth Circuit acknowledged that, as a general proposition, an expert's "fail[ure] to rule out every possible alternative cause . . . *normally* affect[s] the weight . . . and not the admissibility of that testimony." 259 F.3d at 202 (emphasis added). But they ignore the very next two lines of the holding, which make clear that an expert's failure to even consider such alternative causes is appropriate grounds to exclude the expert's testimony:

> "However, a 'differential diagnosis that fails to take serious account of other potential causes may be so lacking that it cannot provide a reliable basis for an opinion on causation.' . . . Thus, if an expert utterly fails to consider alternative causes or fails to offer an explanation for why the proffered alternative cause was not the sole cause, a

district court is justified in excluding the expert's testimony."

Id. (citations omitted); *see also Haller v. AstraZeneca Pharms. LP*, 598 F. Supp. 2d 1271, 1299 n.263 (M.D. Fla. 2009) (finding an expert "must at least adequately consider each proffered alternative cause"). And in fact, in *Cooper*, the Fourth Circuit upheld the district court's decision to exclude the testimony of an expert whose differential diagnosis was unreliable precisely because, like Dr. Murphy, he failed to adequately consider and to rule out a number of potential alternative causes of plaintiff's injury. 259 F.3d at 202-03.

Second, Plaintiffs argue that "it was not necessary" for Dr. Murphy to rule out prediabetes as a potential alternative cause because "Dr. Murphy's opinion [was] that Ms. Hempstead's blood glucose levels were normal, and not prediabetic, before she began taking Lipitor." Opp. at 20. Plaintiffs apparently overlook Dr. Murphy's admission that Ms. Hempstead had at least one blood glucose level in the prediabetic range in 1995, approximately five years before she started taking Lipitor. Murphy Tr. (Ex. 3) at 195:25-196:11. As Dr. Murphy acknowledges in her report, patients with prediabetes have a significantly increased risk of developing diabetes.[4] Murphy Rpt. (Ex. 1) at 5. Similarly, Plaintiffs suggest that "it was not necessary" for Dr. Murphy to consider metabolic syndrome because she "does not investigate this in her clinical practice and does not find it helpful."[5]

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[4] According to the Joslin Diabetes Center at Harvard Medical School, patients with prediabetes "are at high risk of developing type 2 diabetes . . . within a decade *unless* they adopt a healthier lifestyle that includes weight loss and more physical activity." What is Pre-Diabetes?, Joslin Diabetes Center, Harvard Medical School, available at: http://www.joslin.org/info/what_is_pre_diabetes.html (last visited on September 18, 2015) (emphasis in original) (Ex. 27). Ms. Hempstead failed to adopt a healthier lifestyle (and, in fact, gained significant weight) and, not coincidentally, was diagnosed with diabetes in 2004, nine years after her first prediabetic blood glucose value.

[5] Plaintiffs also claim that Dr. Murphy independently considered each of the individual risk factors that together constitute the metabolic syndrome—blood glucose levels, lipids, hypertension and weight. Opp. at 21. In fact, however, Dr. Murphy's report does not contain any discussion of the impact of Ms. Hempstead's pre-Lipitor blood glucose levels and elevated lipids (in particular her high triglycerides) on her diabetes risk.

Opp. at 21. It is unclear how this argument is relevant, given that Dr. Murphy admitted that metabolic syndrome "confer[s] an increased risk" for diabetes.[6] Indeed, the National Institutes of Health specifically state that "a person who has metabolic syndrome is . . . five times as likely to develop diabetes as someone who doesn't have metabolic syndrome."[7]

Finally, and most significantly, Plaintiffs entirely ignore Dr. Murphy's failure to consider, or to rule out, Ms. Hempstead's adult weight gain as a potential alternative cause of her diabetes. At deposition, Dr. Murphy admitted: (1) that Ms. Hempstead gained 24 pounds in the ten years prior to her diabetes diagnosis, Murphy Tr. (Ex. 3) at 244:25-245:2; (2) that such weight gain could be a "contributing cause to the development of [Ms. Hempstead's] diabetes," *id*. at 245:22-246:7; (3) that data from the Nurses' Health Study (which Dr. Murphy describes as providing "the most validated data on risk assessment")[8] shows that such weight gain is associated with a two-fold increased risk of diabetes, *id*. at 244:25-245:13; and (4) that she did not address the role of Ms. Hempstead's weight gain in her expert report, *id*. at 245:14-21. Indeed, Dr. Murphy could not even say whether the contribution of Ms. Hempstead's weight gain was more or less substantial than that of Lipitor:

> Q. Is it possible that the 24-pound weight gain between 1992 and 2004 is the reason that Ms. Hempstead's blood glucose levels went up sufficiently to cause her to be diagnosed with diabetes?
>
> MR. MICELI: Object to the form.

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[6] Murphy Tr. (Ex. 3) at 250:2-3. Plaintiffs' expert Dr. Handshoe acknowledged that metabolic syndrome is a well-recognized, powerful, independent risk factor for diabetes. Handshoe *Daniels* Tr. at 116:24-117:19, 236:3-7 (exhibit filed under seal at Dkt. No. 1004-6, incorporated by reference); Handshoe *Hempstead* Tr. at 176:10-15, 176:21-24 (exhibit filed under seal at Dkt. No. 1004-41, incorporated by reference); *see also* Singh Tr. (Ex. 4) at 216:9, 56:8-13; Gale Tr. (Ex. 2) at 287:15-24.

[7] National Institutes of Health, What Is Metabolic Syndrome?, available at: http://www.nhlbi.nih.gov/health/health-topics/topics/ms (last visited on September 18, 2015) (Ex. 28).

[8] Murphy Rpt. (Ex. 1) at 11.

> THE WITNESS: It could be, as I've said, a contributing cause to the development of her diabetes.
>
> Q. BY MR. BROWN: Could it be a substantial contributing cause, as you have used that term?
>
> A. As a cause, it is less significant than some of the other things. I would say it's not as substantial as some of the other factors.
>
> Q. Is it as substantial as her use of Lipitor?
>
> A. Again, it's hard to quantify the different factors independently.

Id. at 246:1-15. Because Dr. Murphy failed to consider prediabetes, metabolic syndrome, and adult weight gain as potential alternative causes of Ms. Hempstead's diabetes diagnosis, her analysis "cannot provide a reliable basis for an opinion on causation." *Cooper*, 259 F.3d at 202 (citations omitted).[9]

B. Dr. Murphy Did Not Rule Out Those Alternative Causes She Did Consider As Being Sufficient On Their Own to Explain Ms. Hempstead's Diabetes Diagnosis.

Plaintiffs acknowledge that Dr. Murphy did not rule out all of the potential alternative causes of Ms. Hempstead's diabetes but rather "concluded that multiple factors could have contributed" to her disease. Opp. at 5. These include at least four significant alternative causes: age, family history of diabetes, hypertension, and elevated BMI (body mass index). Murphy Rpt. (Ex. 1) at 15; Murphy Tr. (Ex. 3) at 184:12-19; Opp. at 10.

Plaintiffs claim, however, that Dr. Murphy ruled out these contributing factors as sufficient to cause Ms. Hempstead to be diagnosed with diabetes in May of 2004. Opp. at 16-17. Dr. Murphy's

[9] Equally troubling is the glaring inconsistency in Dr. Murphy's testimony. On one hand, Dr. Murphy was not willing to opine that Ms. Hempstead's weight gain was a substantial contributing factor in her developing diabetes, noting that "it's hard to quantify the different factors independently." Murphy Tr. (Ex. 3) at 246:1-15. On the other hand, Dr. Murphy offers the *ipse dixit* opinion that, to a reasonable degree of medical certainty, Lipitor is a substantial contributing factor—this despite the fact that she does not know whether the contribution of Lipitor is greater or smaller than that of Ms. Hempstead's weight gain. This inconsistency in Dr. Murphy's analysis and opinions raises additional red flags concerning the reliability of her methodology and the admissibility of her testimony.

deposition testimony stands at odds with Plaintiffs' assertion. Asked whether she could say that these four factors were not sufficient—taken together or individually—to explain Ms. Hempstead's diabetes diagnosis in May 2004, Dr. Murphy answered: "So again, I haven't said that she couldn't have developed those—diabetes from any one of those or the combination of those alone."[10] Murphy Tr. (Ex. 3) 231:17-19. That is perhaps not surprising as Dr. Murphy testified that patients with the same risk factors as Ms. Hempstead can and do develop diabetes without ever taking Lipitor; in fact, she has seen those patients in her own practice. *Id.* at 232:7-11.

Plaintiffs also claim that Dr. Murphy explained in her report and deposition testimony the "process" by which she ruled out all "other factors as sufficient by themselves to have caused [Ms. Hempstead's] diabetes." Opp. at 17. Neither the references provided by Plaintiffs nor any other place in the record contains such explanation. Indeed, even Dr. Gale—Plaintiffs' expert with thirty years of experience in the diabetes field—testified that it is impossible to do what Plaintiffs would like the Court to believe Dr. Murphy has done:

> Q. When it comes to an individual woman who took Lipitor and was later diagnosed with diabetes, is it possible to determine whether or not she still would have developed diabetes had she not taken Lipitor?
>
> A. No.

Gale Tr. (Ex. 2) at 210:14-19.

To be sure, Dr. Murphy repeatedly stated in her report and deposition that it is her opinion, to a reasonable degree of medical certainty, that, absent taking Lipitor, Ms. Hempstead would not have been diagnosed with diabetes "at the time" (meaning in May 2004). But Dr. Murphy's simply

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[10] *See also* Murphy Tr. (Ex. 3) at 164:5-12 ("Q. And those other risk factors would be sufficient on their own to cause the disease; is that right? MR. MICELI: Object to the form. THE WITNESS: Any person can develop diabetes. So, yes, she, as anyone in this room or any person as far as I know on the planet can develop Type 2 diabetes. So I can't predict or say that she wouldn't have or wouldn't otherwise in the future.").

stating that this is her opinion is not sufficient to satisfy *Daubert*.[11] Absent a reliable, peer-reviewed, and validated method for reaching that conclusion, Dr. Murphy's opinion is nothing more than inadmissible *ipse dixit*. *Daubert v. Merrell Dow Pharms. Inc.*, 509 U.S. 579, 592-93 (1993); *see also Cooper*, 259 F.3d at 203. As the Supreme Court held in *Joiner*, "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). That is exactly the situation here.

As discussed earlier, Ms. Hempstead had blood glucose levels in the prediabetic range approximately five years before she first took Lipitor. According to Dr. Murphy, this means that the "disease process leading to diabetes ha[d] likely begun" by that time. Murphy Rpt. (Ex. 1) at 5. Thus, Ms. Hempstead's pre-existing risk factors were sufficient on their own not only to initiate the diabetes disease process, but also to cause the disease to progress to the point where, in 1995, she already had abnormal blood glucose levels. That invites the question: what methodology does Dr. Murphy have to reliably conclude that those same risk factors were not sufficient—over the course of the next decade (from 1995 until her diagnosis in 2004)—to cause Ms. Hempstead's disease to progress such that her blood glucose rose to a level that met the diagnostic criteria for diabetes? [12] The answer is none.

Nowhere in the record is there any evidence that Dr. Murphy has any such methodology, or

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[11] Casting further doubt on this opinion is the fact that Dr. Murphy does not know when Ms. Hempstead first had diabetes, and admitted that Ms. Hempstead may have had diabetes as early as September 2003, while she was off of Lipitor. Murphy Tr. (Ex. 3) at 215:23-216:1, 210:14-19.

[12] It is important to note that Ms. Hempstead's risk factors did not remain stable throughout this period of time. For example, both her age and weight increased, meaning that her risk of diabetes went up further during that time, entirely independent of her Lipitor use.

that she even attempted to systematically evaluate and answer that question.[13] In fact, when asked at deposition to explain the cause of the changes in Ms. Hempstead's blood glucose levels that preceded her diabetes diagnosis, Dr. Murphy was unable to do so, stating at one point: "I'm not sure that without—I can explain whether, you know, what was going. There's many potential causative factors," Murphy Tr. (Ex. 3) at 199:18-24, and again later: "So, again, as with the increase you were asking me to explain before, I can't, really." *Id.* at 203:23-204:2. Dr. Murphy also acknowledged that she did not have any methodology to evaluate to what extent Ms. Hempstead's various pre-existing risk factors contributed to those blood glucose changes, and never even attempted to conduct such analysis. *Id.* at 207:23-208:3. Perhaps that is why, in the end, the best Dr. Murphy could do by way of explanation was to say that she "feel[s]" that Lipitor "contributed" to the rise in Ms. Hempstead's blood glucose levels and led to her eventual diabetes diagnosis. *Id.* at 206:23-207:8. Dr. Murphy's feelings and "subjective beliefs" are not a substitute for a valid scientific method. *Cooper*, 259 F.3d at 200.

Similarly, Dr. Murphy admitted that she could not quantify the relative contribution of Ms. Hempstead's numerous risk factors to her diabetes, Murphy Tr. (Ex. 3) at 185:21-187:3; could not say whether the effect of Lipitor was greater or smaller than that of Ms. Hempstead's other risk factors, *id.* at 228:15-229:21; or even compare the effect of Lipitor to that of Ms. Hempstead's weight gain (which, as discussed above, Dr. Murphy failed to consider in forming her opinion), *id.* at 246:1-15. Absent a method for quantifying the contribution of Lipitor to Ms. Hempstead's diabetes

[13] Dr. Murphy did state that her opinion is supported by the fact that certain epidemiologic studies—after controlling for some of the same risk factors as Ms. Hempstead had—reported an increased diabetes risk with Lipitor. It is unclear how this fact, even if true and based on reliable data, allows Dr. Murphy to conclude that Ms. Hempstead's other risk factors were not sufficient to cause her, or any other patient for that matter, to develop diabetes. At best, such studies, if conducted in a similar population and at the relevant dose, could provide a basis for Dr. Murphy to rule in Lipitor as a potential cause. They provide no evidence relevant to specific causation.

and blood glucose changes and comparing that contribution to her other risk factors, it is difficult to imagine how Dr. Murphy could reliably rule out those other factors as sufficient, or conclude that Ms. Hempstead would not have been diagnosed with diabetes in May 2004 absent taking Lipitor. *See Haller*, 598 F. Supp. 2d at 1280, 1285, 1299 (excluding an expert who claimed that he ruled out other factors—including hypertension—as the "sole cause" of the plaintiff's diabetes, despite having failed to "quantify the contribution" of those factors to the plaintiff's condition). That is especially true given that Plaintiffs' general causation experts testified that any effect of Lipitor pales in comparison to Ms. Hempstead's other diabetes risk factors, such as age, obesity, family history, and ethnicity. *See* Gale Tr. (Ex. 2) at 136:24-137:7, 133:18-23; Singh Tr. (Ex. 4) at 222:12-22.

As the Fourth Circuit explained in *Oglesby*, "[a] reliable expert opinion must be based on scientific, technical, or other specialized *knowledge* and not on belief or speculation, and inferences must be derived using scientific or other valid methods." *Oglesby v. General Motors Corp.*, 190 F.3d 244, 250 (4th Cir. 1999) (emphasis in original). Because Dr. Murphy's opinion that Ms. Hempstead would not have been diagnosed with diabetes in May 2004 absent taking Lipitor is based on "belief" and "speculation" rather than a valid scientific method, her testimony is not reliable under *Daubert* and should properly be excluded.

C. Dr. Murphy Did Not Reliably Rule In Lipitor As a Potential Cause of Ms. Hempstead's Diabetes.

Plaintiffs claim that Dr. Murphy "ruled in" Lipitor as a potential cause of Ms. Hempstead's diabetes "when she considered whether Lipitor can cause disease and concluded that it can." Opp. at 9. Even if that were true, and Dr. Murphy reliably concluded that Lipitor is capable of causing diabetes in some patients at some dose, that does not mean that she reliably ruled in Lipitor as a potential cause in this case. In order to do so, Dr. Murphy must come forward with reliable evidence that Lipitor is capable of causing diabetes when used at the dose taken by Ms. Hempstead, *i.e.*, 20

mg. In other words, the evidence Dr. Murphy relies on to rule in Lipitor must "fit" the specific facts of this case. *Daubert*, 509 U.S. at 591.

Dr. Murphy does not do so. In her report, Dr. Murphy does not cite any data indicating that Lipitor, when taken at the 20 mg dose, statistically significantly increases diabetes risk. Nor does she indicate that she is relying on any of Plaintiffs' other experts for such opinion. Absent a reliable basis to conclude that Lipitor at the 20 mg dose increases the risk of diabetes, Dr. Murphy cannot reliably rule in Lipitor as a potential cause of Ms. Hempstead's condition. *See McClain*, 401 F.3d at 1242 (noting that "dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect").

Furthermore, in forming her opinion that "Lipitor significantly increases blood glucose levels which can lead to new onset diabetes," Dr. Murphy places significant weight on a Women's Health Initiative observational study by Culver,[14] noting in her report that the study provides some of the "most validated data on risk assessment" and that the study has "particular relevance" to Ms. Hempstead's case. Murphy Rpt. (Ex. 1) at 6, 11, 16. Dr. Murphy specifically references a hazard ratio of 1.61 from the study, a risk estimate which she considers to be "a pretty good ballpark" of the magnitude of the risk conveyed by Lipitor. *Id*. at 6; Murphy Tr. (Ex. 3) at 45:15-46:1; *see also id*. at 48:1-2 ("the *most reliable data* suggests the risk ratio is somewhere around 1.6") (emphasis added). For a number of reasons, the Culver study does not provide a reliable basis to rule in Lipitor as a potential cause of Ms. Hempstead's diabetes.[15]

First, the study did not specifically evaluate Lipitor at the 20 mg dose. Second, Plaintiffs'

[14] A.L. Culver et al., *Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative*. Arch Intern Med, 2012;172:144-152 ("Culver") (Ex. 29).

[15] As discussed in Pfizer's general causation briefing currently pending before the Court, none of the other data and analyses Dr. Murphy cites in her report provide reliable evidence that Lipitor use increases diabetes risk. *See* Pfizer's Motion to Exclude Plaintiffs' Expert Testimony on the Issue of General Causation and Memorandum in Support, [ECF No. 972].

experts acknowledge that observational studies which do not adjust for major diabetes risk factors cannot provide reliable evidence about the relationship between Lipitor use and diabetes risk. *See, e.g.*, Singh Tr. (Ex. 4) at 224:11-25; Gale Tr. (Ex. 2) at 221:15-223:23. As Dr. Singh, whom Plaintiffs describe as their "primary general causation expert," acknowledged, the Culver study did not adjust for hypertension, elevated fasting glucose, low HDL, metabolic syndrome, and impaired glucose tolerance, Singh Tr. (Ex. 4) at 232:2-7, all of which are known diabetes risk factors and many of which Ms. Hempstead had prior to starting Lipitor.[16] Finally, the study authors did not have baseline blood glucose data for the majority of the study participants, and thus could not rule out that those patients had diabetes before they ever took Lipitor. When the risk analysis was limited to the subset of patients who did not have diabetes at baseline and for whom fasting blood glucose data was available, statin use was not associated with an increased risk of diabetes.[17] Accordingly, the Culver study does not provide reliable evidence that Lipitor increases diabetes risk in patients like Ms. Hempstead.

II. DR. MURPHY'S SPECIFIC CAUSATION OPINION IS BASED ENTIRELY ON THE PRESENCE OF A TEMPORAL RELATIONSHIP.

Plaintiffs spend more than four pages of their brief arguing that Dr. Murphy's opinion is "not based solely on a temporal relationship." Opp. at 12-16. The record says otherwise.

Dr. Murphy explained her approach to evaluating causation in an individual case early in her deposition:

> I would try and establish that there's background evidence that there is an increased risk of diabetes with Lipitor in larger studies. And then in that individual, did the diabetes appear after the Lipitor was given? And—and I then look at the risk and whether or not the Lipitor was given and whether or not the patient took the Lipitor,

[16] Ms. Hempstead had hypertension, Murphy Rpt. (Ex. 1) at 13; elevated fasting glucose, Murphy Tr. (Ex. 3) at 195:25-196:11; low HDL, *id*. at 251:14-17; and metabolic syndrome; *id*. at 251:18-252:13.

[17] Culver (Ex. 29) at 147.

> and then with the background risk, I'm able to attribute that as a causative factor in their development of diabetes.

Murphy Tr. (Ex. 3) at 123:1-11. Later in the day, when asked to identify the evidence that supported her opinion that Lipitor contributed to Ms. Hempstead's diabetes, Dr. Murphy again explained that the basis of her opinion was a temporal relationship: "I think what we've outlined here, she – there's a temporal relationship with her taking the Lipitor. There's evidence that she took the Lipitor. There's an increased risk of diabetes with Lipitor, and then she developed diabetes." *Id*. at 188:6-13. Dr. Murphy's testimony is clear. The only case specific evidence she relied on to support her opinion in this case is the presence of a temporal relationship between Ms. Hempstead's Lipitor use and her diabetes diagnosis.[18]

While they understandably devote a lot of space to this issue, Plaintiffs fail to identify any case specific data, other than the presence of a temporal relationship, that support Dr. Murphy's causation opinion. In fact, Plaintiffs concede that no direct evidence exists—in the form of laboratory tests, markers, or other clinical data—indicating that Lipitor contributed in any way to Ms. Hempstead's diabetes.[19] Opp. at 15. And Plaintiffs make clear that Dr. Murphy's analysis of Ms. Hempstead's blood glucose data simply "support[s] the temporal relationship between the Lipitor use and Plaintiff's development of diabetes." Opp. at 16.

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[18] Dr. Murphy's opinion that there is an increased risk of diabetes with Lipitor is not a case specific fact; it goes to the issue of general causation which is addressed in separate briefing now before the Court. Neither Dr. Murphy nor Plaintiffs claim that an increased risk of diabetes in epidemiologic studies (even if reliably established) is sufficient to conclude specific causation in an individual patient. If that were the case, Dr. Murphy would necessarily offer the opinion that Lipitor caused diabetes in every patient who took Lipitor and later was diagnosed with diabetes—an opinion that Plaintiffs vehemently argue Dr. Murphy is not willing to offer. Opp. at 14-15.

[19] Indeed, as Pfizer explained in its opening brief, Dr. Murphy conceded that she has no evidence that Lipitor caused any injury to Ms. Hempstead's pancreas, Murphy Tr. (Ex. 3) at 190:21-191:1, and that there is no biomarker or fingerprint indicating that Lipitor played any role in her diabetes disease process. *Id*. at 152:4-8, 188:16-18.

Instead, Plaintiffs claim, citing to the Fourth Circuit's decision in *Westberry*, that the presence of a temporal relationship provides "compelling evidence of causation" in her case. Opp. at 13-14. Nothing could be further from the truth. To begin with, as Pfizer stated in its opening brief, Plaintiffs' own experts disagree with this assertion. *See* Singh. Tr. (Ex. 4) at 355:25-356:5; Quon Tr. (Ex. 5) at 85:22-86:5, 75:8-12. Furthermore, the facts in *Westberry* are entirely distinguishable from those here. In *Westberry*, the Fourth Circuit acknowledged that "the mere fact that two events correspond in time does not mean that the two necessarily are related in any causative fashion," but held that, under a very specific set of circumstances, the presence of a temporal relationship can provide compelling evidence of causation.[20] *Westberry*, 178 F.3d at 265. In that case, there was evidence that the plaintiff's alleged injury (a sinus condition) developed shortly after he was exposed to the putative causative agent (in that case talc) and improved when the plaintiff removed himself from the exposure (what is sometimes referred to as challenge/dechallenge evidence). *Id.* None of those facts are present here.

First of all, Ms. Hempstead was not diagnosed with diabetes until about four years after she started taking Lipitor. Thus, unlike *Westberry*, this is not a case where the initiation of the disease process occurred in close proximity to exposure. Second, Ms. Hempstead's blood glucose levels actually were better (lower) two years after she started Lipitor than they were before she took the medication, Murphy Tr. (Ex. 3) at 203:3-9, indicating that Lipitor "did not appear to have . . . an effect on increasing her glucose level." *Id*. at 202:21-203:17. Third, when Ms. Hempstead stopped taking Lipitor for three weeks, her blood glucose levels actually got worse, reaching the highest level she had experienced to that point. *Id*. at 209:14-25. Indeed, Dr. Murphy testified that Ms.

[20] Absent such unique circumstances, courts repeatedly have held that temporal proximity is entitled to little weight in determining causation. *See, e.g., McClain*, 401 F.3d at 1243; *Bland v. Verizon Wireless, (VAW) L.L.C.*, 538 F.3d 893, 898-99 (8th Cir. 2008); *Moore v. Ashland Chem. Inc.*, 151 F.3d 269, 278 (5th Cir. 1998).

Hempstead may actually have had diabetes at that time. *Id*. at 210:14-19. Finally, Ms. Hempstead has had "excellent blood glucose control" over the past eleven years since her diagnosis, despite continuing treatment with Lipitor and even increasing her dose. Murphy Rpt. (Ex. 1) at 11. Thus, the facts here are easily distinguishable from those in *Westberry* and, if anything, raise questions as to whether a temporal relationship even exists.

The facts here are actually much closer to those in *Guinn*, where the plaintiff was diagnosed with diabetes four years after starting treatment with Seroquel. 602 F.3d at 1254. In its decision, specifically distinguishing *Westberry*, the Eleventh Circuit held that evidence of temporal proximity was "especially unreliable" in that context. *Id*. In reaching that conclusion, the court emphasized the fact that diabetes develops gradually over many years and that many patients have diabetes for a number of years prior to being diagnosed. *Id*. As Pfizer noted in its opening brief, Dr. Murphy and Plaintiffs' other experts have offered similar testimony, acknowledging that diabetes may take a decade or more to develop and "can often be present for months to years before it is diagnosed." Murphy Rpt. (Ex. 1) at 5; *see also* Quon Tr. (Ex. 5) 240:3-24; Gale Tr. (Ex. 2) at 159:2-4, 175:7-18, 184:1-13. Thus, here, like in *Guinn*, the presence of a vague temporal relationship—the only case specific evidence Dr. Murphy offers in support of her opinion that Lipitor was a substantial contributing cause in Ms. Hempstead developing diabetes—does not provide any reliable evidence of causation.

Because Dr. Murphy failed to provide reliable evidence that Lipitor played any role in Ms. Hempstead's diabetes, her testimony should be excluded. *See Cooper*, 259 F.3d at 201.

CONCLUSION

For the foregoing reasons, and those discussed in its opening brief, Pfizer respectfully requests that this Court exclude the opinions of Plaintiffs' expert Dr. Elizabeth J. Murphy.

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CERTIFICATE OF SERVICE

I hereby certify that, this 18th day of September, 2015, I have electronically filed a copy of the above and foregoing with Clerk of the Court using the ECF system, which sent notification of such filing to counsel of record.

/s/ Mark S. Cheffo